Cognition and Physical Disability in Predicting Health-Related Quality of Life in Multiple Sclerosis

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Many studies have shown that multiple sclerosis (MS) has a significant impact on patient health-related quality of life (HRQOL), but the relative contributions of physical versus cognitive disability are not well established. Most studies have relied on HRQOL outcomes that depend largely on patient mood, life satisfaction, and personal happiness. The Sickness Impact Profile (SIP) is a measure of HRQOL known for its relatively strong emphasis on task completion and activities of daily living. As such, the SIP may be less influenced by depression. We sought to determine the relative influence of physical disability and cognition, above and beyond demographic and disease variables, in predicting HRQOL. Patients (n = 132) and healthy controls (n = 26) underwent complete neuropsychological evaluation using the Minimal Assessment of Cognitive Function in MS (MACFIMS) battery and a series of self-report measures assessing depression, fatigue, and HRQOL. The SIP was also administered. Correlation analysis and group comparisons revealed significant associations between cognition and HRQOL outcomes. Logistic regression models comparing the Expanded Disability Status Scale (EDSS) and cognitive tests in predicting poor physical HRQOL retained both EDSS and Symbol Digit Modalities Test (SDMT) performance, while models predicting poor psychosocial and poor overall HRQOL retained only the SDMT. These findings support cognition as a significant predictor of overall HRQOL, psychosocial HRQOL, and, interestingly, physical HRQOL. ***Int J MS Care.*** **2011;13:57–63.**

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system with a variable and broad range of physical, psychological, and cognitive symptoms. It is widely recognized that MS can have a significant impact on a patient's health-related quality of life (HRQOL)[1]—that is, their happiness or satisfaction in meaningful daily activity despite the disease.[2] However, research in this area has often failed to account for the numerous disease and clinical features of MS, leading to a lack of consensus as to the most important predictors of reduced HRQOL in this population.[3,4] This problem is of great interest in the comprehensive care of MS patients, particularly as HRQOL and adjustment to illness may help predict disease progression[4] (eg, through influencing susceptibility to relapses, engagement in positive health behaviors, use of active coping strategies, and so on). Previous research in MS has shown associations between poor HRQOL and progressive disease course,[5-9] greater physical disability,[10-15] disease duration,[10] fatigue,[11,12,16,17] and depression.[3,6,17-21] Of these, physical and cognitive capacity are measured by performance-based reliable measures, and it is not clear which ability domain is most critical for poor HRQOL in MS patients. Many studies have shown cognitive impairment to be a predictor of reduced HRQOL,[10,22-25] while others have not supported this association.[26]

Given the increasing attention to HRQOL across medical and psychological illnesses, an abundance of HRQOL measures are available, both generic and disease-specific. One of the most popular generic HRQOL measures, the 36-item Short Form Health Status Survey (SF-36),[27] generates physical and mental component

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scores based on the patient's perception of his or her health status. One of the most commonly employed MS-specific HRQOL measures, the Multiple Sclerosis Quality of Life–54 (MSQOL-54),[28] adds 18 MS-specific items to the original SF-36. While allowing for greater sensitivity in within-disease comparison,[29] the MSQOL-54 is again based on the patient's subjective report of life satisfaction. For example, patients are asked to rate how much time they have felt "discouraged" (item 38) and "weighed down" (item 41) by their illness, and item 33 presents sad and happy facial expressions along a 10-point scale and directs patients to rate their overall "quality of life."

In contrast, although it is a self-report survey, the Sickness Impact Profile (SIP)[30,31] is based largely on judgments of the frequency of instrumental behaviors and the capacity to complete a diverse range of activities of daily living. Without the emphasis on subjective satisfaction, the SIP may be less likely to be influenced by depression. In emphasizing the capacity to engage in activities, the SIP allows a more concrete appraisal of activity. Patients are asked to read a series of statements and indicate those that are applicable to them. Examples of items from each SIP subscale are presented in Table 1. The SIP items range from mild ("I go up and down stairs more slowly") to more severe ("I do not walk at all") disability and yield physical and psychosocial dimension scores, in addition to a total score representing overall disability.

The SIP is widely used and well validated in a wide range of disease populations[31] and has been used in several studies in MS as a behaviorally based measure of HRQOL.[15,21,32-36] In one study employing both the SIP and the SF-36, the SIP was shown to have stronger associations with the Multiple Sclerosis Functional Composite (MSFC) and EDSS than the SF-36.[34] Using the SIP, our objective was to determine the relative influence of physical disability and cognitive impairment in predicting HRQOL in a large sample of MS patients. Controlling for demographic and disease characteristics, including depression and fatigue, our outcomes were physical, psychosocial, and overall HRQOL.

Table 1. Sickness Impact Profile: item examples

Subscale	Item example
Sleep and rest	I am sleeping or dozing most of the time, day and night.
Emotional behavior	I often moan and groan in pain or discomfort.
Body care and movement	I stand only for short periods of time.
Home management	I am not doing heavy work around the house.
Mobility	I stay away from home only for brief periods of time.
Social interaction	I am cutting down on the length of visits with friends.
Ambulation	I walk shorter distances or stop to rest often.
Alertness behavior	I react slowly to things that are said or done.
Communication	I have difficulty speaking, for example, get stuck, stutter, stammer, slur my words.
Work	I am not accomplishing as much as usual at work.
Recreation and pastimes	I am doing more inactive pastimes in place of my other usual activities.
Eating	I am eating much less than usual.

Methods

Participants

The study sample included 132 MS patients and 26 healthy controls recruited at an MS care center in the eastern United States. All participants provided informed consent to be included in the study as per institutional review board requirements. Exclusion criteria for MS patients were 1) current or past medical or psychiatric disorder other than MS that could affect cognitive function, 2) current substance abuse, 3) neurological impairment that might interfere with psychometric testing, and 4) MS relapse or corticosteroid pulse within 6 weeks of neuropsychological testing.

For the MS group, the mean (SD) age was 46.4 (10.3) years and the mean amount of education was 14.4 (2.1) years. The majority of the sample (73%) was female and white (90%). The mean disease duration was 11.7 (8.3) years. Diagnosis and MS course were based on established guidelines for research protocols in MS[37] (relapsing-remitting [RR] = 94; secondary progressive [SP] = 38). The median EDSS[38] score was 3.5 (range = 0–6.5), obtained within 6 months of neuropsychological testing for all patients. Controls had a mean age of 43.6 (11.5) years and a mean amount of education of 15.0 (2.0) years. The majority (58%) were female and white (89%).

Tests and Study Procedures

All patients and controls underwent complete neuropsychological evaluation using the Minimal Assessment of Cognitive Function in MS (MACFIMS) battery[39,40] and a series of self-report measures. The Controlled Oral Word Association Test (COWAT)[41] assessed verbal fluency and consisted of three 60-second trials in which the participant generated as many words as possible beginning with a designated letter of the alphabet. The Judgment of Line Orientation (JLO) test[42] measured visual/spatial processing and required participants to accurately match the position and direction of two unlabeled lines to two lines on a labeled model. The California Verbal Learning Test, second edition (CVLT2)[43] measured verbal learning and memory. During the learning phase a word list was presented and participants recalled the list five times consecutively and following a delay period. The Brief Visuospatial Memory Test–Revised (BVMTR)[44] assessed visual/spatial learning and memory. During the learning phase a display containing abstract geometric figures was presented. Participants reproduced as many figures as possible on each of three learning trials and following a 25-minute delay period. Rao's adaptations[45] of the Symbol Digit Modalities Test (SDMT)[46] and Paced Auditory Serial Addition Test (PASAT 3.0 and 2.0)[47] were used to measure mental processing speed and working memory. The SDMT required participants to voice the number associated with a random array of target symbols defined by a key at the top of the page. The PASAT presented a series of single-digit numbers and required participants to add each new digit to the one immediately preceding it; digits were presented at a rate of one every 3 seconds on the first trial and every 2 seconds on the second trial. Finally, the Delis-Kaplan Executive Function System (DKEFS)[48] Sorting Test was employed to measure executive function. Participants were given six cards and asked to sort the cards into two groups and to verbally describe the sorting principle applied.

Self-report measures included the Beck Depression Inventory–Fast Screen (BDIFS),[49] Fatigue Severity Scale (FSS),[50] and SIP.[30] The SIP total and dimension scores range from 0 to 100, with higher scores reflecting greater dysfunction and a score of 20 indicating severe dysfunction or the need for substantial daily care.[51-53]

Statistical Analyses

Statistical analyses were conducted using SPSS, version 18.0 (SPSS, Chicago, IL). The MS and control groups were compared on demographic and predictor variables using univariate analysis of variance (ANOVA). Relationships between individual cognitive tests and HRQOL variables were then examined in the patient group using partial correlations controlling for age and education. Based on diagnostic criteria for the MACFIMS battery,[39] MS patients were also broadly classified as cognitively normal or cognitively impaired (two or more cognitive test z scores of −1.5 or less), and HRQOL total, dimension, and category scores were evaluated.

As total and dimension scores on the SIP were not normally distributed, the measure was dichotomized using the above-described cutoff score of 20 to indicate poor HRQOL. Logistic regression models were then used to determine whether cognition or physical disability better predicts HRQOL. We included three models, controlling for the effects of age, education, sex, disease course, disease duration, BDIFS, and FSS. The models were designed to predict patients with poor versus good HRQOL using the SIP physical dimension, SIP psychosocial dimension, and SIP total score, while controlling for subjectively reported emotional distress and fatigue. We selected the EDSS as the measure of physical disability, and CVLT2 delayed recall, BVMTR delayed recall, SDMT, and PASAT 3.0 raw scores as potential cognitive predictors, as these tests represent the most commonly seen cognitive deficits in MS, episodic memory and processing speed, respectively.[39,54] In each model, the first block consisted of demographic variables, BDIFS, and FSS. The second block consisted of EDSS and cognitive test scores using a forward stepwise selection procedure with P to enter = .05 and P to exit = .10.

Results

Group (MS vs. healthy control) differences in age and education were not statistically significant (Table 2). As expected, MS patients had lower HRQOL in the SIP physical dimension ($P < .001$), SIP psychosocial dimension ($P < .001$), and SIP total score ($P < .001$), as well as lower performance on all cognitive tests except the JLO. MS patients also reported greater fatigue ($P < .001$), and there was a trend for more depression in the MS group ($P < .10$).

Table 2. Demographic, HRQOL, and cognitive characteristics for MS and control groups

	MS (n = 132)	Healthy control (n = 26)	*P*
Age, y	46.4 (10.3)	43.6 (11.5)	NS
Education, y	14.4 (2.1)	15.0 (2.0)	NS
BDIFS	3.0 (3.4)	1.9 (1.9)	<.10
FSS	5.0 (1.5)	2.8 (1.0)	<.001
SIP total score	16.9 (13.4)	1.0 (1.8)	<.001
SIP physical dimension	13.6 (13.0)	0.5 (2.0)	<.001
SIP psychosocial dimension	16.5 (16.0)	1.4 (3.0)	<.001
COWAT	34.5 (11.5)	41.7 (9.3)	<.01
JLO	22.2 (5.8)	24.5 (3.3)	<.10
CVLT2 total learning	51.6 (12.8)	63.4 (8.1)	<.001
CVLT2 delayed recall	11.0 (3.6)	13.4 (1.7)	<.001
BVMTR total learning	19.4 (7.0)	26.5 (4.1)	<.001
BVMTR delayed recall	7.6 (2.7)	10.1 (1.5)	<.001
SDMT	49.0 (15.2)	63.4 (9.0)	<.001
PASAT 3.0	41.1 (15.0)	48.5 (9.6)	<.05
PASAT 2.0	29.9 (12.9)	38.8 (8.3)	<.01
DKEFS correct sorts	9.4 (3.0)	11.7 (2.4)	<.001
DKEFS description score	35.1 (11.7)	45.0 (9.8)	<.001

Abbreviations: BDIFS, Beck Depression Inventory–Fast Screen; BVMTR, Brief Visuospatial Memory Test–Revised; COWAT, Controlled Oral Word Association Test; CVLT2, California Verbal Learning Test, second edition; DKEFS, Delis-Kaplan Executive Function System; FSS, Fatigue Severity Scale; HRQOL, health-related quality of life; JLO, Judgment of Line Orientation; MS, multiple sclerosis; NS, not significant; PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol Digit Modalities Test; SIP, Sickness Impact Profile.
Note: Values are given as mean (SD).

Table 3 shows partial correlations between cognitive tests and HRQOL outcomes. When controlling for the effects of age and education, lower performance on cognitive tests was associated with worse HRQOL. All cognitive tests except the JLO were significantly associated with SIP total, physical, and psychosocial domains. The data reveal small to medium correlations, with somewhat larger correlations between cognition and physical versus psychosocial HRQOL.

Patients were classified by overall cognitive status. Group differences in HRQOL between cognitively normal and cognitively impaired MS patients are shown in Table 4. MS patients classified as cognitively impaired reported significantly lower HRQOL in the SIP physical dimension ($P < .001$), SIP psychosocial dimension ($P < .01$), and SIP total score ($P < .001$), as well as lower HRQOL in all individual SIP categories except emotional behavior.

Table 3. Partial correlations between cognitive and HRQOL measures controlling for age and education

	SIP total	SIP physical	SIP psychosocial
COWAT	−0.298[a]	−0.274[a]	−0.190[b]
JLO	NS	NS	NS
CVLT2 total learning	−0.265[a]	−0.244[a]	−0.220[b]
CVLT2 delayed recall	−0.244[a]	−0.263[a]	−0.196[b]
BVMTR total learning	−0.324[a]	−0.324[a]	−0.287[a]
BVMTR delayed recall	−0.342[a]	−0.353[a]	−0.299[a]
SDMT	−0.429[a]	−0.462[a]	−0.250[a]
PASAT 3.0	−0.306[a]	−0.326[a]	−0.230[a]
PASAT 2.0	−0.348[a]	−0.323[a]	−0.219[b]
DKEFS correct sorts	−0.337[a]	−0.379[a]	−0.241[a]
DKEFS description score	−0.288[a]	−0.341[a]	−0.203[b]

Abbreviations: BVMTR, Brief Visuospatial Memory Test–Revised; COWAT, Controlled Oral Word Association Test; CVLT2, California Verbal Learning Test, second edition; DKEFS, Delis-Kaplan Executive Function System; HRQOL, health-related quality of life; JLO, Judgment of Line Orientation; NS, not significant; PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol Digit Modalities Test; SIP, Sickness Impact Profile.
[a] $P < .01$.
[b] $P < .05$.

Logistic regression models predicting poor HRQOL in the SIP physical dimension retained both EDSS (Wald = 7.25, $P < .01$) and SDMT (Wald = 7.50, $P < .01$), correctly classifying 79% of patients. Poor HRQOL in the SIP psychosocial dimension was significantly predicted only by SDMT (Wald = 9.70, $P < .001$), correctly classifying 82% of patients. Finally, the model predicting poor HRQOL in the SIP total score retained only the SDMT (Wald = 13.98, $P < .001$), correctly classifying 81% of patients.

Discussion

The primary objective of this study was to evaluate the relative predictive value of physical and cognitive disability in HRQOL among MS patients while controlling for demographic and subjective distress variables, including depression and fatigue. We selected the SIP as our measure of HRQOL based on its emphasis on specific behaviors and abilities versus patient perception

Table 4. Comparison of HRQOL between cognitively normal and cognitively impaired MS patients

SIP variable	Normal (n = 46)	Impaired (n = 86)	*P*	*d*
Total score	11.2 (12.0)	19.89 (13.2)	<.001	0.68
Physical dimension	8.2 (10.8)	16.6 (13.0)	<.001	0.68
Psychosocial dimension	10.6 (12.6)	19.6 (16.8)	<.01	0.58
Sleep and rest	15.9 (20.2)	24.9 (26.3)	<.05	0.37
Emotional behavior	13.0 (17.0)	15.0 (19.0)	NS	—
Body care and movement	7.2 (10.8)	15.7 (14.3)	<.01	0.64
Home management	12.4 (16.0)	23.0 (19.9)	<.01	0.57
Mobility	5.4 (10.3)	12.0 (14.6)	<.01	0.49
Social interaction	8.2 (10.6)	15.0 (16.6)	<.01	0.46
Ambulation	12.9 (16.7)	22.7 (17.4)	<.01	0.57
Alertness behavior	23.9 (27.6)	41.4 (32.0)	<.01	0.57
Communication	5.7 (11.8)	14.9 (18.0)	<.01	0.57
Work	25.1 (31.1)	46.0 (30.7)	<.001	0.68
Recreation and pastimes	17.6 (20.5)	30.5 (21.7)	<.01	0.61
Eating	0.8 (2.8)	2.9 (5.4)	<.01	0.45

Abbreviations: HRQOL, health-related quality of life; MS, multiple sclerosis; NS, not significant.
Note: Values are given as mean (SD).

of health or disease status. Interestingly, while the EDSS was first to enter the regression model predicting poor physical HRQOL, cognitive impairment as represented by poor SDMT score was also retained in this model. Only the SDMT was retained in the models predicting psychosocial and overall HRQOL, with lower scores on the SDMT significantly predicting poor psychosocial HRQOL and poor overall HRQOL. Our data regarding the EDSS and its relationship with physical components of HRQOL are consistent with previous research,[10-15] while the meaning of cognition as a predictor warrants further exploration. The findings suggest the possibility of a greater role for cognitive impairment in HRQOL among MS patients, and require replication in larger patient samples with other HRQOL outcomes.

The finding that cognition plays a role in physical HRQOL is interesting, and suggests that beyond actual physical capability, cognition may have a significant impact on one's ability to engage in meaningful physical activities. For example, MS patients who are cognitively impaired may be more likely to experience falls or may require more assistance with physical activities of daily living than patients with equal physical disability but without cognitive impairment. Although walking has customarily been understood as a largely automatic motor task, recent evidence suggests the involvement of higher-order cognitive processing and control of gait.[55,56] Associations between walking speed and measures of executive function and attention have been shown in young and older adult populations,[56-58] patients with traumatic brain injury,[59] Parkinson's disease,[60] and Alzheimer's disease.[61] Further research is necessary to understand the connection seen in these data between poor physical HRQOL and cognitive impairment, including variables that might mediate that relationship, such as personality factors.

The only SIP subscale for which there was no abnormality in MS was emotional behavior. Relatively speaking, the SIP would seem to measure a person's perception of instrumental capacity more than their happiness or satisfaction with activities and lifestyle. This is not to say that the latter dimension is not important. For example, many MS patients may be happier after they come to accept that they cannot walk after 20 years with MS than when they are suffering from depression and fatigue in the beginning stages of the disease. The relative importance of the SIP versus more conventional measures of HRQOL such as the MSQOL-54 in terms of prognosis and risk for complications of the disease remains to be seen.

Table 4 reveals that with the exception of SIP summary scores, the greatest area of disability was reported to be in the area of vocation status. We have previously addressed vocational disability and its predictors.[3] In that large cross-sectional study of 120 MS patients, cognitive status was a primary predictor over and above depression, subjectively reported fatigue, EDSS score, and psychiatric symptoms. More recently, we have identified degrees of deterioration on specific cognitive tests that place patients at high risk for vocational disability, such as a 4-point loss on the SDMT.[62]

Our findings indicate that mental processing speed may influence a wide range of daily activities, including recreational activity, social interaction, task completion, and workplace demands. In multiple dimensions of HRQOL, greater cognitive impairment is associated with worse functioning and diminished activity. This highlights the broad range of physical, emotional, psychological, and social domains affected by cognitive impairment and the importance of early detection and management of cognitive symptoms in MS. Accurate and timely characterization of cognitive impairment in MS may have implications for patient and caregiver education, potential coping/compensation strategies, and therapeutic interventions aimed at improving patient HRQOL. Cognitive rehabilitation and training efforts have shown mixed outcomes in MS,[63-65] but recent evidence suggests that intensive and domain-specific cognitive training in attention, processing speed, and executive function is effective.[66] Behavioral interventions may include referrals for speech therapy or occupational therapy, and pharmacological interventions are under continued investigation for efficacy in treating cognitive impairment in MS. □

PracticePoints

- Multiple sclerosis (MS) is well known to have a significant impact on patient health-related quality of life (HRQOL). Yet the relative value of cognitive and physical impairment in predicting HRQOL in MS is not well established.
- Surprisingly, in addition to physical disability, cognition emerges as a significant predictor of physical HRQOL, suggesting that cognition may affect the patient's ability to engage in meaningful physical activity. Only cognition significantly predicted psychosocial and overall HRQOL, with lower cognitive test scores predicting worse HRQOL.
- The association between cognition and HRQOL domains in MS highlights the importance of early identification of cognitive impairment in the comprehensive care of MS patients.

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